In vivo and in vitro biotransformation of the lithium salt of gamma-linolenic acid by three human carcinomas.

Br J Cancer. 1997;75(12):1812-8.

de Antueno R, Elliot M, Ells G, Quiroga P, Jenkins K, Horrobin D.

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Lipid metabolism has been considered recently as a novel target for cancer therapy. In this field, lithium gamma-linolenate (LiGLA) is a promising experimental compound for use in the treatment of human tumours. In vivo and in vitro studies allowed us to assess the metabolism of radiolabelled LiGLA by tumour tissue and different organs of the host. In vitro studies demonstrated that human pancreatic (AsPC-1), prostatic (PC-3) and mammary carcinoma (ZR-75-1) cells were capable of elongating GLA from LiGLA to dihomo-gamma-linolenic acid (DGLA) and further desaturating it to arachidonic acid (AA). AsPC-1 cells showed the lowest delta5-desaturase activity on DGLA. In the in vivo studies, nude mice bearing the human carcinomas were given Li[1-(14)C]GLA (2.5 mg kg(-1)) by intravenous injection for 30 min. Mice were either sacrificed after infusion or left for up to 96 h recovery before sacrifice. In general, the organs showed a maximum uptake of radioactivity 30 min after the infusion started (t = 0). Thereafter, in major organs the percentage of injected radioactivity per g of tissue declined below 1% 96 h after infusion. In kidney, brain, testes/ovaries and all three tumour tissues, labelling remained constant throughout the experiment. The ratio of radioactivity in liver to tumour tissues ranged between 16- and 24-fold at t = 0 and between 3.1- and 3.7-fold at 96 h. All tissues showed a progressive increase in the proportion of radioactivity associated with AA with a concomitant decrease in radiolabelled GLA as the time after infusion increased. DGLA declined rapidly in liver and plasma, but at a much slower rate in brain and malignant tissue. Seventy-two hours after the infusion, GLA was only detected in plasma and tumour tissue. The sum of GLA + DGLA varied among tumour tissues, but it remained 2-4 times higher than in liver and plasma. In brain, DGLA is the major contributor to the sum of these fatty acids. Data showed that cytotoxic GLA and DGLA, the latter provided either by the host or by endogenous synthesis, remained in human tumours for at least 4 days.

The effects of n-6 polyunsaturated fatty acids on the expression of nm-23 in human cancer cells.

Br J Cancer. 1998 Mar;77(5):731-8.

Jiang WG, **Hiscox S**, **Bryce RP**, **Horrobin DF**, **Mansel RE**.

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This study examined the effect of n-6 polyunsaturated fatty acids (PUFAs) on the expression of nm-23, a metastasis-suppressor gene, in two highly invasive human cancer cell lines, HT115 and MDA MB 231. A range of n-6 and n-3 PUFAs were tested. We report that while linoleic acid and arachidonic acid reduced the expression of nm-23-H1, gamma linolenic acid (GLA) and its soluble lithium salt markedly increased the expression of the molecules. The stimulation of the expression of nm-23 by GLA was seen at both protein and mRNA levels. Up-regulation of nm-23 was also associated with a reduction of the in vitro invasiveness of these cells. It is concluded that gamma linolenic acid (GLA) enhances the expression of nm-23. This contributes to the inhibition of the in vitro invasion of tumour cells.

Growth inhibitory effect of lithium gamma linolenate on pancreatic cancer cell lines: the influence of albumin and iron.

Eur J Cancer. 1998 Jan;34(1):188-92.

Ravichandran D, **Cooper A**, **Johnson CD**.

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Essential fatty acids, especially gamma linolenic (GLA) and eicosapentaenoic acids, have been proposed as potential anticancer drugs. Our aim was to study the effect of the lithium salt of gamma linolenic acid (LiGLA) on the growth of two human pancreatic cancer cell lines (MIA PaCa2 and Panc 1) and primary human fibroblasts (HFF 5) in vitro. Cell growth was assessed by a microculture tetrazolium (MTT) assay. LiGLA had a selective growth inhibitory effect on pancreatic cancer cell lines with 50% growth inhibition (IC50) at approximately 6-16 mumol/l compared with approximately 111 mumol/l for the fibroblasts. The degree of growth inhibition increased with the time of exposure to LiGLA. Special attention was paid to the influence of albumin and iron on LiGLA-mediated growth inhibition. Albumin incorporated into essentially serum-free culture medium inhibited the effect of LiGLA in a dose-dependent manner, associated with reduced GLA uptake by cancer cells. Ferric ions were confirmed as potentiators of the growth inhibitory effect of LiGLA but more physiologically relevant transferrin-bound iron was ineffective. With further improvements in the fatty acid delivery mechanism, LiGLA may become a useful adjunct in the management of pancreatic cancer patients.

Effect of [redacted] on the growth of experimental human pancreatic carcinoma.

Br J Surg. 1998 Sep;85(9):1201-5.

Ravichandran D, **Cooper A**, **Johnson CD**.

University Surgical Unit, Southampton General Hospital, UK.

BACKGROUND: [redacted] is growth inhibitory to pancreatic cancer cells in vitro and is reported to prolong the survival of patients with pancreatic cancer. The effect of Li-GLA on the growth of human pancreatic carcinoma in vivo is not known. In this study the effect of parenterally administered Li-GLA on the growth of human pancreatic carcinoma in nude mice was tested. METHODS: Pancreatic tumours were produced in nude mice by subcutaneous implantation of MIA PaCa-2 cells. This cell line is sensitive to Li-GLA in vitro. Mice were randomly treated with intraperitoneal, intravenous or intratumoral Li-GLA. Each group also had controls. RESULTS: Both intravenous and intraperitoneal administration of Li-GLA had no significant effect on tumour growth or tumour phospholipid fatty acid composition. Intratumoral administration of Li-GLA was, however, associated with a significant antitumour effect. CONCLUSION: Within the limitations of this tumour model, the benefit seen with intravenous Li-GLA in patients with pancreatic carcinoma cannot be explained by tumour growth inhibition. Local administration appears to be more effective than intravenous or intraperitoneal therapy.

A preliminary study on intravenous infusion of [redacted].

Drug Dev Ind Pharm. 2000 Feb;26(2):189-91.

Liu Y, **Chen D**.

Department of Surgery, Rui-Jin Hospital, Shanghai No. 2 Medical University, China.

[redacted]
(50 micrograms/ml), were used for intravenous infusion. In a preclinical study in dogs, Na-EPA lowered the activity of transminases (glutamic pyruvic transaminase [GPT], glytamic oxaloacetic transaminase [GOT]); however, Na-AA increased the activity of GPT and GOT. In the clinical study, the numbers of leukocytes and lymphocytes of volunteers increased and remained at that level for 3 to 5 days after intravenous infusion. The study indicated that an intravenous infusion of Na-EPA may have anti-inflammatory and immunomodulatory effects.

Comparative anti-mitotic effects of lithium gamma-linolenate, gamma-linolenic acid and arachidonic acid, on transformed and embryonic cells.

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Department of Physiology, University of Pretoria, South Africa.

The effects of gamma-linolenic acid (GLA), the lithium salt of gamma-linolenic acid (LiGLA) and arachidonic acid (AA) were compared at doses of 50 microg/ml for periods of 6 and 24 h on cell cycle progression and apoptosis induction in transformed and in normal cells. In WHCO3 (oesophageal cancer) cells and on primary embryonic equine lung cells, we found LiGLA to be the most effective in apoptosis induction. After 24 h, 94% of the WHCO3 cancer cells and 44% of the primary embryonic equine lung cells exposed to LiGLA were apoptotic. The WHCO3 cancer cells were also very susceptible to the apoptosis-inducing effects of AA (56%) and GLA (44%), whereas the embryonic equine lung cells were much less affected by these two fatty acids. After 6 h exposure to all three compounds, most of the cycling WHCO3 cancer cells were blocked in S-phase. After 24 h treatment, some of the S-phase cells exposed to AA and GLA were apparently able to move into the G2/M phase, the LiGLA exposed cells were mostly apoptotic and no cycling cells were present. The primary embryonic equine lung cells were fairly resistant to the cytotoxic effects of GLA and AA. From our studies we conclude that, although LiGLA was the most toxic to the cancer cells, it is apparently less selective, compared to AA and GLA, in the killing of cancer and normal cells. It would also appear that the lithium might have added to the cytotoxic effects of LiGLA. The mechanism needs to be clarified.

An open-label phase I/II dose escalation study of the treatment of pancreatic cancer using lithium gammalinolenate.

Anticancer Res. 1996 Mar-Apr;16(2):867-74.

Fearon KC, Falconer JS, Ross JA, Carter DC, Hunter JO, Reynolds PD, Tuffnell Q.

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There are currently no satisfactory treatments for inoperable pancreatic cancer. Median survivals for untreated patients are of the order of 100 days and, with one exception, no chemotherapy or radiotherapy regime has been found to produce a worthwhile extension of life with reasonably tolerable side effects. Gamma-linolenic acid (GLA) has been found to kill about 40 different human cancer cell lines in vitro without harming normal cells. The lithium salt of GLA (LiGLA) can be administered intravenously and a dose escalation study of a 10 day infusion followed by oral therapy in patients with inoperable pancreatic cancer was carried out in 48 patients in two centres. Peripheral venous infusion caused thrombophlebitis but this could be avoided by infusing via a central vein with appropriate heparinisation. Too rapid infusion caused haemolysis which could be avoided by slow dose escalation in the first few days and maintenance of plasma lithium below 0.8 mmol/l. Doses ranged from 7 to 77g/patient cumulatively delivered over 2-12 days. Other than the above described events there were no important side effects and patients felt well during the infusions. A Kaplan-Meier analysis showed that survival was not significantly influenced by which centre the patients were treated in, the sex of the patients or the presence or absence of histological confirmation. The presence or absence of liver metastases, the patients' Karnofsky scores and the-dose of LiGLA had significant effects on survival from treatment. A Cox proportional hazards model revealed similar results: in both centres, in both sexes, and in patients with and without liver metastases according to the model the highest doses of LiGLA were associated with longer survival times as compared with the lowest doses. LiGLA deserves investigation in a randomised prospective study.

[The spermicidal activity of fish oil, [redacted]

Shengzhi Yu Biyun. 1987 Aug;7(3):24-8.
[Article in Chinese]

Wang JZ, Lou YB, Zhu RL, Chen PD.

PIP: The chief polyunsaturated fatty acids and unsaturated acids known to exist in fish oil are: [redacted] linoleic acid, oleic acid, and docosenoic acid. They have been made into emulsions of pluronic F68-physiological saline and sodium salts physiological saline solutions. Following that, the action of their spermicidal activities in vitro occurred. Emulsion and sodium salt solutions of docosahexaenoic acid had the strongest spermicidal activity observed. The most efficient concentration was 0.001 mM, similar to that of propranolol. In line for most efficient after that were eicosapentaenoic acid, arachidonic acid, oleic acid, and docosenoic acid. The experimental results indicated that the spermicidal activity of fatty acid was intensified with the increase of the unsaturated bond. Besides, the most efficient concentration of either morrhuic acid or sodium morrhuate was 0.1%. Therefore, they contained more docosahexaenoic acid and eicosapentaenoic acid and were ideal spermicides in vitro. The spermicidal mechanism of fatty acids may be related to the potential action of the carboxyl group. (author's modified)

Vopr Pitan. 1968 Jul-Aug;27(4):82-3. Related Articles, Links

[The effect of [redacted] on the course of experimental atherosclerosis in rabbits]

[Article in Russian]

Novikova NA.

PMID: 5700257 [PubMed - indexed for MEDLINE]

Sb Lek. 1968 Oct;70(10):307-13. Related Articles, Links

[Competition between bilirubin and sodium oleate, bromsulphatalein and bile salts as regards bonds with albumin, assessed by gel filtration on sephadex G25]

[Article in Czech]

Kucerova L, Hoenig V.

PMID: 5697170 [PubMed - indexed for MEDLINE]

Q J Exp Physiol Cogn Med Sci. 1973 Jul;58(3):267-74. Related Articles, Links

Stimulation of afferent nerve terminals in the perfused rabbit liver by sodium salts of some long chain fatty acids.

Orbach J, Andrews WH.

PMID: 4489893 [PubMed - indexed for MEDLINE]

Am J Dig Dis. 1973 Dec;18(12):1067-74. Related Articles, Links

The effect of sodium oleate on cholesterol solubility in bile salt-lecithin model systems.

Inoue T, Juniper K Jr.

PMID: 4761528 [PubMed - indexed for MEDLINE]

[redacted] induced cytotoxicity against cells chronically infected with HIV-1.

FEBS Lett. 1993 Sep 13;330(2):219-21.

Kinchington D, **Randall S**, **Winther M**, **Horrobin D**.

Department of Virology, Medical College of St. Bartholomew's Hospital, West Smithfield, London, UK.

Lithium gamma-linolenate (Li-GLA), was evaluated for its activity in selectively killing H9 cells chronically infected with HIV-1RF. After 4 days incubation with Li-GLA approximately 90% of the H9RF cells were non-viable compared to 20% of uninfected H9 cells. The efficacy of the Li-GLA, in preferentially killing HIV infected cells also correlates with lipid peroxidation, as measured by the intracellular thiobarbituric acid-reactive material content. The addition of an antioxidant (vitamin E) to the culture medium reduced the toxicity of Li-GLA. These data indicate that this selective killing effect of cells chronically infected with HIV may be due to the enhanced extent of lipid peroxidation of the added Li-GLA.

The effect of [redacted] therapy of pancreatic cancer on perfusion in liver and pancreatic tissues.
Pancreas. 1998 Jan;16(1):105-6.
Kairemo KJ, **Jekunen AP**, **Korppi-Tommola ET**, **Pyrhonen SO**.

Publication Types:

- Letter

PMID: 9436871 [PubMed - indexed for MEDLINE]

Comparative anti-mitotic effects of [redacted], gamma-linolenic acid and arachidonic acid, on transformed and embryonic cells.

Prostaglandins Leukot Essent Fatty Acids. 1998 Oct;59(4):285-91.

Seegers JC, **Lottering ML**, **Panzer A**, **Bianchi P**, **Stark JH**.

Department of Physiology, University of Pretoria, South Africa.

The effects of gamma-linolenic acid (GLA), the [redacted] were compared at doses of 50 microg/ml for periods of 6 and 24 h on cell cycle progression and apoptosis induction in transformed and in normal cells. In WHCO3 (oesophageal cancer) cells and on primary embryonic equine lung cells, we found LiGLA to be the most effective in apoptosis induction. After 24 h, 94% of the WHCO3 cancer cells and 44% of the primary embryonic equine lung cells exposed to LiGLA were apoptotic. The WHCO3 cancer cells were also very susceptible to the apoptosis-inducing effects of AA (56%) and GLA (44%), whereas the embryonic equine lung cells were much less affected by these two fatty acids. After 6 h exposure to all three compounds, most of the cycling WHCO3 cancer cells were blocked in S-phase. After 24 h treatment, some of the S-phase cells exposed to AA and GLA were apparently able to move into the G2/M phase, the LiGLA exposed cells were mostly apoptotic and no cycling cells were present. The primary embryonic equine lung cells were fairly resistant to the cytotoxic effects of GLA and AA. From our studies we conclude that, although LiGLA was the most toxic to the cancer cells, it is apparently less selective, compared to AA and GLA, in the killing of cancer and normal cells. It would also appear that the lithium might have added to the cytotoxic effects of LiGLA. The mechanism needs to be clarified.

PMID: 9849656 [PubMed - indexed for MEDLINE]